REMARKS

The Examiner's objection to Claims 1, 3-6, 8-11 and 15 under 35 U.S.C. 112 is not understood. In view of the specification "functionally equivalent to active p53" is completely clear.

A word the Examiner seems to be missing or misunderstanding is the word "active." p53 has a negative regulatory domain that turns the cellular functions on and off. p53as lacks that domain and is thus always "active."

Another word the Examiner seems to be misunderstanding is "functionally." The function referred to is cellular function and especially "growth regulator" function, not whether or not it can be recognized by an extraneous antibody having little or nothing to do with cellular function.

The statement on pages 2 and 3 of the specification describing "growth regulatory function" and the statement that p53as "functions" the same as p53as is completely adequate under 35 U.S.C. 112. One skilled in the art clearly knows that what is being referred to is cell regulatory function. Any other interpretation of "functionally equivalent" would be meaningless and inconsistent with the specification since antigenic differences between p53 and p53as are pointed out in detail in the specification. "Functionally equivalent" is thus clearly not intended to mean antigenically equivalent.

A patent application is not supposed to be a textbook of what is already known to those skilled in the art. Cellular function of p53, as opposed to antigenic nature (which is not really a function at all) is described in many known documents. The Examiner is

referred to the numerous documents cited in the original Information Disclosure Statement and the supplemental Information Disclosure Statement accompanying this response.

In the interest of advancing prosecution, the claims have nevertheless been amended to limit "functionally" to "growth control functionally".

The specification has been amended to place the sequence I.D.'s in all caps.

The Examiner is correct that "p53" in the last lines of Claims 1 and 5 should have been maintained as "p53as." The Applicant's records have been corrected accordingly.

The Examiner has rejected Claims 1 and 5 under 35 U.S.C. 112 on the ground that the specification does not disclose or contemplate inclusion of epitopes in general to give rise to a p53as specific antibody. The Applicant respectfully disagrees. The specification clearly teaches that the final 50 carboxy terminal amino acids may be modified or completely eliminated while maintaining p53 function. It is further clearly taught that an epitope unique to p53as may be incorporated within those final 50 carboxy terminal amino acids.

One skilled in the art is clearly capable of selecting a unique epitope for inclusion at the terminal end of p53as and such is supported by the specification.

On page 2, the specification says that the p53as may be synthetic and almost simultaneously says that p53as is essentially identical to known normal growth controlling protein p53, at least until the final 50 amino acids at the carboxy end. There is no reasonable interpretation other than that modifications may be synthetically made

only at the final 50 amino acids of p53. There is no other location where the desired epitope can be placed.

There is no ambiguity and there is support for the present claims.

The Examiner has rejected Claims 1, 3-6, 8-11 and 15 under 35 U.S.C. 112. This rejection should be withdrawn. It is clearly taught that the final 50 amino acids may be truncated to remove the negative regulatory domain from p53 and obtain a perpetually active p53 (p53as without identifying epitope).

An identifying epitope can clearly be added to truncated p53 per the specification (to obtain synthetic p53as). The only place such modification is permitted is within the final 50 amino acids of p53 which permits continued p53 function. Almost any epitope can be synthetically added because the epitope sequence is in reality functionally separate from the active p53 sequence, i.e., a truncated p53 functions without any addition at all.

It is, of course, possible that an added epitope could be so long that it sterically interferes with p53 function. One skilled in the art would know not to make such excessively large substitutions because large substitutions are not necessary to obtain a unique epitope and because large substitutions could risk activity. However, even if large substitutions were made, it is easy enough for one skilled in the art to test for retained p53 activity.

Contrary to the Examiner's position, there is thus precise teaching that modification of p53 should be within its final 50 amino acids. One skilled in the art would certainly not select an epitope size so large as to sterically hinder p53 activity and in any case such activity can be easily tested. Since a truncated p53 is active it would be

expected that almost any reasonably sized unique epitope could be attached to a truncated p53 without adversely affecting activity. If activity was for some reason unexpectedly affected another unique epitope could be easily selected.

Undue experimentation would not be required.

The Examiner has rejected Claims 16-18 under 35 U.S.C. 112 on the ground that the claim is not limited to the raising of antibodies to Sequence I.D. No. 1. With due respect to the Examiner, grammatically Claim 16 refers to the raising of an antibody by Sequence I.D. No. 1 because "Sequence I.D. No. 1" is the subject of the comma separated clause. However, in the interest of advancing prosecution, Claim 16 has been amended to remove any possible ambiguity.

Claims 1, 3, 4 and 15 have been rejected as being anticipated by Wolf et al. as evidenced by Arai et al. The Applicant again asserts that the combination of references cannot be used for a rejection under 35 U.S.C. 102.

Wolf et al. apparently does not refer to a plasmid but rather to a clone. There is no reason to look to Arai et al. to find a plasmid even under 35 U.S.C. 103, and certainly not under 35 U.S.C. 102.

M-8 does not appear to be a plasmid as asserted by the Examiner but rather a clone designation. Wolf et al. suggest a plasmid for no purpose and Arai et al. only suggests one for purposes of assay, i.e., pSP65.

Claims 1, 3, 4 and 15 have been rejected under 35 U.S.C. 102 as being anticipated by Arai et al.

The Applicant again asserts that M-8 is not the same as and does not suggest p53as.

As previously discussed the present claims require that p53as be functionally equivalent to active p53. The sequence disclosed by Arai et al. and Wolf et al. does not meet that very critical requirement.

The mutant p53 disclosed by Arai et al. is not suggested by either Arai et al. or Wolf et al. as being active at all. Neither Arai et al. nor Wolf et al. suggest that the Arai et al. sequence is present in normal cellular environments. Arai et al. obtained his structure from chemically transformed cells, not from normal cells. "Transformation" in the present application does not refer to chemical transformation. The amino acid sequence predicted (not prepared or isolated) by Arai et al. and referred to by the Examiner, is not a p53as terminal sequence, but is embedded. It would not be a separate peptide, even if translated (translation is not suggested by Arai et al.). Furthermore, the entire Arai et al. sequence is not a p53as. The final nucleic acids of the encoding sequence of Arai et al. sequence is not a p53as. The final nucleic acids of the encoding sequence of Arai et al. simply do not match the encoding sequence of p53as of either naturally occurring p53 or naturally occurring p53as.

claims 15, 16, & 19 only

Regard. of claims

Please note that the mutant clone of Arai et al. is distinct from p53 and p53as in structure and function. In structure, it has a mutation of the p53 gene coding region whereby a cyst residue at amino acid 132 is replaced by a phe residue. See Arai et al, 1986, page 3236 for entire coding sequence of p53-M-8 with the change noted. This alone is enough to prevent Arai et al. from anticipating the present claims since the

claims of the present application do not permit such an embedded variation. The pending claims require that the p53 and p53as sequences must be identical up to the carboxy terminus. This is necessary for p53as to retain p53 functionality. Arai et al. and Wolf et al. do not meet this requirement.

In function, the Arai et al. (Wolf et al.) M-8 mutant clone lacks the functionality of both p53 and p53as. This is completely contrary to the requirements of the present claims.

p53as has the properties of p53 including:

1. binding efficiently and specifically to the p53 consensus sequence in DNA and forming tetramers (see Kulesz-Martin et al., Mol. Cell. Bio., pp 1698-1708, March 1994, and Wu et al., EMBO, Vol. 13, pp 4823-4830, 1994) and

2. transcriptional activation suppression of growth (Wu et al., PNAS, pp 8982-8987, August 1997).

By contrast M-8 does not have the functionality of either p53 or p53as, but has its own deviant characteristics including:

1. transforming cells, rather than suppressing transformation (Eliyahu et al., Oncogene 3:313-321, 1998), and

2. forming monomers and dimers, not tetramers (Hainaut and Milner, EMBO 11:3513-3520, 1992).

Arai et al. (Wolf et al.) simply does not have a sequence which is the same as p53 up to the final 50 carboxy terminal amino acids, and does not have functionality similar to active p53 as required by the present claims. The Applicants have cited respected

literature references showing these differences. In the absence of at least equally strong rebuttal evidence, the Examiner should withdraw these rejections. There is absolutely no reason or suggestion given by Arai et al. or Wolf et al. for incorporating a complete and functional p53as cDNA into a vector. Such a suggestion can only be obtained from the present application by impermissible hindsight.

The Examiner asserts that objective evidence that M-8 and p53as are different has not been provided.

The references referred to above and in the prior response are cited and provided in either the original or Supplemental Information Disclosure Statement. These references clearly show M-8 and p53as are not functionally equivalent to either p53 or p53as.

This is all that is necessary to show that both Wolf et al. and Arai et al. are irrelevant to the present invention.

New Claims 16 and 17 are patentable over Wolf et al. and Arai et al. whether considered alone or in combination. As previously discussed and shown by the cited references, Wolf et al. and Arai et al. are irrelevant to the present invention. M-8 does not have the functionality of either p53 or p53as.

The Examiner has rejected Claims 5, 6, 8-11 and 15-18 under 35 U.S.C. 103 as being unpatentable over Wolf et al. or Arai et al. in view of Lee et al.

This rejection is in error and should be withdrawn.

The basis for the Examiner's rejection is that "plasmid constructs of the p53as molecule were known in the art (Wolf et al., Arai et al.) and Lee et al. was cited to show

that cloning of known sequences into baculoviral vectors was art standard technology. The premises of the rejection are faulty for several reasons. First of all, for the reasons previously discussed, none of Wolf et al., or Arai et al. disclose or suggest plasmid constructs of the p53as molecule. Secondly, none of these references or their combination suggest any reason for making such a plasmid construct. And thirdly, even if such a suggestion were made, which it is not, it is a leap of logic with no documentary support, to say that placing a p53as cDNA sequence in a plasmid (with no reason given for doing so) makes it obvious to put such a sequence into a virus. The cited references must show more than technical feasibility. They must suggest a reason for engaging in the combining technology for the particular sequence in question. There are billions of things that are technically feasible but there is no reason to do them unless there is a reasonable end purpose. None of the cited references or their combination give such a purpose which can only be obtained from the present application by impermissible hindsight.

Claims 1, 3-6, 8-11 and 15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al. in view of Lee et al.

This rejection is a hindsight rejection and should be withdrawn. Han et al. teaches incorporation of "segments" into a plasmid for purposes of characterization. Placing a whole p53as chain into a plasmid would be counterproductive since sequencing would thus be made very difficult or impossible. Han et al. teaches away from the present invention. No function of a p53as is suggested by Han et al. that would warrant placing a

p53as into a plasmid and certain no purpose is suggested for such a p53as plasmid combination.

Lee et al. adds nothing to Han et al.

Lee et al. is a disclosure for incorporation of DNA unrelated to p53as into viral vectors. Lee et al. suggests no function of p53as warranting its introduction into a viral vector. Combining Han et al. with Lee et al. is a hindsight combination since neither suggests any purpose for selecting p53as DNA, from among billions of DNA sequences, for incorporation into a vector.

In view of the foregoing amendments and remarks it is asserted that all claims are in condition for allowance, which action is courteously requested.

Respectfully submitted,

Dated: May 10, 1999

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